Docket No.: 30694/41506
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Orit Kollet et al.

Application No.: 10/552,299 | Confirmation No.: 2069

Filed: August 25, 2006 | Art Unit: 1632

For: Stem Cells Having Increased Sensitivity to SDF-1 and Methods of Generating and Using Same | Examiner: W. C. W. Shen

RESPONSE TO INTERVIEW SUMMARY AND SUPPLEMENTAL RESPONSE TO OFFICE ACTION MAILED MARCH 1, 2011

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants acknowledge the Interview Summary dated August 3, 2011 (hereinafter "the Summary"). Pursuant to M.P.E.P. §713.04, Applicants invite the Examiner to check the accuracy of this interview summary response and respond to the same, as appropriate. This written reply is being filed before the one-month time frame indicated in the Summary. It is believed that no fee is due with this paper.

On July 28, 2011, Examiner Shen and Applicants' representatives, William K. Merkel, Ph.D. and Lance M. Shaner, Ph.D., discussed the 35 U.S.C. § 103(a) rejection of record over Rafii et al. (U.S. Pat. Pub. No. 20040071687; hereinafter "Rafii") in view of Fisher et al. (*Biochem*, 41(26):8289-97 (2002); hereinafter "Fisher"), Mohle et al. (*Blood*, 91(10):3283-91 (2001); hereinafter "Mohle") and Kollet et al. (*Blood*, 97(10), 3283-91 (2001); hereinafter "Kollet"), documented on pages 4-14 of the outstanding non-final office action mailed March 1, 2011. As noted above, Examiner Shen communicated the Summary to Applicants on August 3, 2011. The Summary accurately reflected the overall topics of

discussion. In particular, Applicants explained that a *prima facie* case of obviousness under § 103(a) had not been established because the Examiner did not show that the cited art disclosed or suggested each claim-recited element, did not provide a reason to modify or to combine the disclosures of Rafii and Kollet, and did not establish that one of skill would have had a reasonable expectation of success in practicing the claimed subject matter. In the interview, Applicants further explained that the reason for maintaining that none of the three requirements for a *prima facie* case of obviousness had been satisfied was because of a complete lack of reasoned support for the rejection in the Office Action. In addition, the Examiner stated in the Interview Summary that "Kollet et al. teaches that the expression of CXCR4 is increased in the hematopoietic stem cells during the process of hematopoietic stem cells mobilization from bone marrow upon induction by chemoattractant SDF-1." This asserted teaching was not discussed during the interview and is not an accurate characterization of Kollet.

The inaccuracies in the Examiner's characterization include the assertions that Kollet (1) deals with the process of HSC mobilization and (2) that SDF-1 was shown to induce CXCR4 expression. This erroneous view of Kollet was one of the reasons that Applicants sought relief in a pre-appeal proceeding. More particularly, on July 6, 2010, Applicants filed a Pre-Appeal Conference Submission based, in part, on the erroneous characterization of Kollet as showing that SDF-1 induced CXCR4 expression, which was asserted in the final Office Action dated January 20, 2010 and the Advisory Action dated June 1, 2010. See Pre-Appeal Conference Submission, pp. 2-3 (hereinafter "the Submission"). It was noted in the Submission that Kollet disclosed that pretreatment of the stem cells *in vitro* with SCF (not SDF-1) and IL-6 induced increased surface expression of CXCR4 and migration toward SDF-1. *Id.* at p. 3. The erroneous assertion that Kollet teaches SDF-1 increasing CXCR4 expression was not repeated in the most recent Office Action and was not discussed during the interview. As a result of the Submission, prosecution was reopened. See Notice of Panel Decision from Pre-Appeal Brief Review mailed August 24, 2010.

The Examiner's characterization of Kollet is also inaccurate in asserting that Kollet discloses a process of HSC mobilization. Kollet actually discloses a process of stem

cell homing. In its Introduction at p. 3283, left column, Kollet states that "[h]ematopoietic stem cells are functionally defined, based on their ability to home to the BM [bone marrow] microenvironment . . . ." In the first sentence of the Results at p. 3285, left column, Kollet reveals that "[t]he homing kinetics of human CB $CD34^{+}$- enriched cells in transplanted NOD/SCID mice were studied." Consistently, Applicants' specification defines homing as "the set of molecular interactions that allows circulating HSCs to recognize, adhere to, and migrate across bone marrow endothelial cells resulting in the accumulation of HSCs in the unique hematopoiesis-promoting microenvironment of the bone marrow." See p. 2, lines 15-18. Thus, Kollet and the instant specification agree that stem cell homing means stem cells that can adhere to and migrate across bone marrow endothelial cells to accumulate in the bone marrow.

In contrast to Kollet and the instant application, Rafii is directed to stem cell mobilization—a process distinct from homing. As noted in paragraph [0097] of Rafii, "bone marrow suppression results in a timely up-regulation of MMP-9 *within the bone marrow microenvironment* with the release of sKitL. . . MMP-9 activation also facilitates mobilization of bone marrow repopulating cells *into the peripheral circulation.*" (Emphases added). Thus, Rafii is directed to the process of stem cell exit from the bone marrow, *i.e.*, mobilization. Accordingly, the Examiner's conclusion in the Summary that "the teachings by Kollet et al. provides specific details that corresponds to the upper part of the diagram shown in Figure 16 taught by Rafii et al." is not accurate, because Rafii's mobilization pathway disclosed in Fig. 16 does not relate to Kollet's homing disclosures.

The M.P.E.P. states that "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." M.P.E.P. § 2143.01(V). As noted above, Rafii is directed to mobilization of stem cells out of the bone marrow microenvironment. For example, claim 1 of Rafii recites "[a] method for recruitment of adult stem cells in an animal comprising administering to the animal a protease or an activator of a protease, wherein the recruitment translocates an endogenous population of quiescent non-cycling stem cells to a permissive vascular zone in the animal so that the stem cells can proliferate, self-renew, differentiate or mobilize to a target site." (Emphasis added.) Thus,

Rafii teaches that MMP-9 is administered to an animal to mobilize an endogenous population of stem cells from the bone marrow into circulation. In contrast, the pending claims are directed to a method of generating stem cells suitable for transplantation, which the specification defines as stem cells capable of efficient homing. See p. 2, lines 9-10. The Examiner has proposed a modification to Rafii, *i.e.*, modifying its disclosed mobilization method (HSC egress from bone marrow) to a homing method (HSC ingress to bone marrow and other organs). Such modifications would defeat the purpose of Rafii's method in promoting HSC ingress rather than egress from the bone marrow. The modification would render Rafii's method unsatisfactory for its intended purpose, *i.e.*, mobilization of stem cells from the bone marrow to circulation. Thus, the Examiner has not provided a motivation to combine the disclosures of Rafii and Kollet to arrive at the claimed subject matter. Neither of the two additional references cited by the Examiner, *i.e.*, Fisher and Mohle, was cited as remedying this defect. Accordingly, the rejections under 35 U.S.C. § 103(a) should be withdrawn.

Additional distinctions of the claimed subject matter over the cited art are also apparent. None of the cited art (Rafii, Kollet, Fisher, and/or Mohle) disclose what would happen to stem cells that are collected and exposed to a matrix metalloprotease *ex vivo*. Additionally, none of Rafii, Kollet, Fisher, or Mohle disclose a role for MMP-9 in stem cell homing. If anything, Rafii teaches away from the claimed methods because, based on the disclosure of Rafii, a person of ordinary skill in the art would not have expected that exposure of stem cells to a matrix metalloprotease would generate stem cells suitable for transplantation, *i.e.*, stem cells that home to, and accumulate in, the unique hematopoiesis-promoting microenvironment of the bone marrow. Instead, if a person of skill in the art would have had any expectation at all, it would have been that exposure of collected stem cells to a matrix metalloprotease would cause the stem cells to mobilize and remain in circulation or migrate away from the bone marrow, rather than home to the bone marrow.

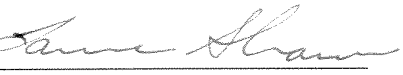
Finally, it is noted that the pathway proposed by Rafii and relied upon by the Examiner encompasses and depends upon components supplied by the bone marrow microenvironment, *e.g.*, sKitL from stromal cells. See Rafii, Figure 16. Thus, the pathway proposed by Rafii is not relevant to the pending claims, which are directed to exposure of

collected stem cells to a matrix metalloprotease (*i.e.*, *ex vivo* treatment), not to *in vivo* treatment of stem cells present in the bone marrow, which have not been collected. Thus, Rafii does not and cannot provide a basis for any expectation regarding the behavior of collected (*i.e.*, isolated) stem cells to a matrix metalloprotease.

Applicants request entry of this paper into the record, and consideration thereof. In view of the Amendment in Response to Non-Final Office Action filed August 1, 2011, and the instant Response to Interview Summary and Supplemental Response, Applicants believe that the pending application is in condition for allowance. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions that might be efficiently resolved in that manner.

Dated: August 17, 2011

Respectfully submitted,

By 

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